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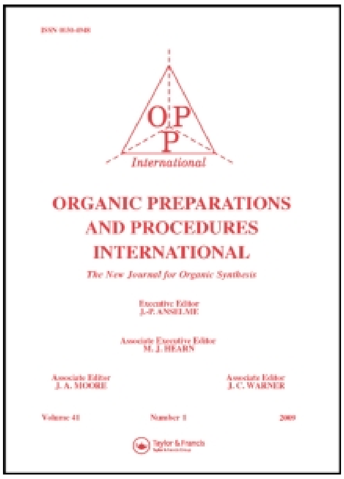

Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

Aromatization of 1,3-Cyclohexanediones Mediated by *bis*-(Trichloromethyl) Carbonate/DMF System

X. R. Liang[a]; F. Shi[a]; R. E. Chen[a]; W. K. Su[a]
[a] Key Laboratory of Pharmaceutical Engineering of Ministry of Education, College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou, P. R. China

Online publication date: 21 July 2010

To cite this Article Liang, X. R. , Shi, F. , Chen, R. E. and Su, W. K.(2010) 'Aromatization of 1,3-Cyclohexanediones Mediated by *bis*-(Trichloromethyl) Carbonate/DMF System', Organic Preparations and Procedures International, 42: 4, 379 — 385

To link to this Article: DOI: 10.1080/00304948.2010.495692

URL: http://dx.doi.org/10.1080/00304948.2010.495692

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Organic Preparations and Procedures International, 42:379–385, 2010

ISSN: 0030-4948 print
DOI: 10.1080/00304948.2010.495692

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Aromatization of 1,3-Cyclohexanediones Mediated by *bis*-(Trichloromethyl) Carbonate/DMF System

X. R. Liang, F. Shi, R. E. Chen, and W. K. Su

Key Laboratory of Pharmaceutical Engineering of Ministry of Education,
College of Pharmaceutical Sciences, Zhejiang University of Technology
Hangzhou, P. R. China

The synthetic potential of the versatile Vilsmeier reaction has been known for years, and been widely applied in the preparation of medicinal compounds, pesticides, dyestuffs, etc.[1–3] Traditionally, Vilsmeier salts have been generated from phosphorus oxychloride ($POCl_3$) and *N*,*N*-dimethylformamide (DMF). Recently, the potential utilization of Vilsmeier salts derived from the *bis*(trichloromethyl) carbonate (BTC)/*N*,*N*-dimethylformamide (DMF) system has been explored extensively.[4] In our previous work, new applications of the BTC Vilsmeier reagent were developed for the preparation of a number of important pharmaceutical intermediates,[5–9] and we now report a new application of the same Vilsmeier reagent for the transformation of 1,3-cyclohexanediones into polysubstituted chlorobenzaldehydes, some of which are of great importance not only in synthesis but also in biological and industrial applications.[10–12] However, to our best knowledge, the synthesis of these compounds from 1,3-cyclohexanediones has only rarely been reported.[10–14]

Initially we investigated for the aromatization reaction using 1,3-cyclohexanedione (**1a**) as model substrate with BTC/DMF under various conditions. The aromatization of 1,3-cyclohexanediones, as reported in the literature,[15–20] generally leads to the formation of complex products.[13,14] In our initial study, the results obtained when 1,3-cyclohexanedione (**1a**) was used are shown in *Table 1*.

Table 1 indicates that the ratio of reagents affect the type of products formed. When one equivalent of **1a** was treated with one equivalent of Vilsmeier reagent (0.33 equivalent of BTC and 1.0 equivalent of DMF) in refluxing 1,2-dichloroethane for 4 h, 3-chlorocyclohex-2-enone (**2**) was formed in 28% yield; 2,4-dichlorobenzaldehyde (**3**) and 2,4-dichlorobenzene-1,3,5-tricarbaldehyde (**4a**) were formed in 42% and 54% yield upon treatment with excess Vilsmeier reagent (*Entries 2 and 3, Table 1*). Lower yields were

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Submitted January 9, 2009.

Address correspondence to W. K. Su, Key Laboratory of Pharmaceutical Engineering of Ministry of Education, College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, P. R. China. E-mail: suweike@zjut.edu.cn

Table 1

Effect of the Ratio of Reagents on Aromatization of **1a**[a]

Entry	Ratio of BTC : DMF : **1a**	Solvent	Conditions	Product	Yield (%)[b]
1	0.33 : 1 : 1	$(CH_2Cl)_2$	Reflux, 4h	**2**	28
2	1 : 3 : 1	$(CH_2Cl)_2$	Reflux, 4h	**3**	42
3	1.67 : 5 : 1	$(CH_2Cl)_2$	Reflux, 4h	**4a**	54

[a] Two mmol of compound **1a** were used.
[b] Yields based on **1a**.

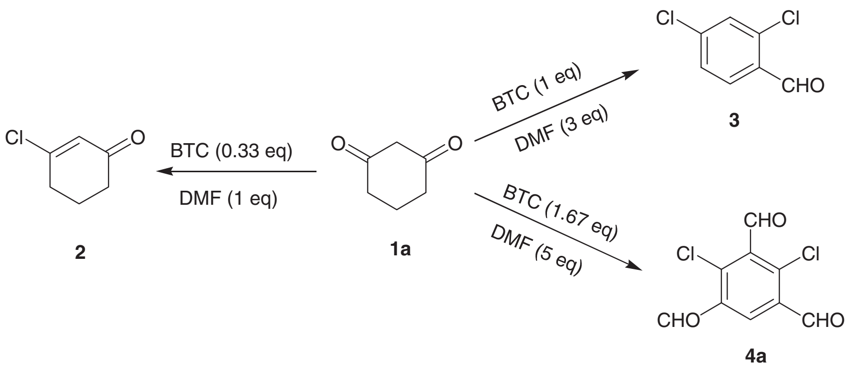
obtained when methylene chloride, DMF and THF were used as solvents. Although **4a** was also formed (in lower yields) from similar treatment of substituted 1,3-cyclohexanediones (*Table 2*, *Entries 2–4*), several by-products were also generated from **1e–g**. Surprisingly, 2,4-dichlorobenzaldehyde (**3**) was the only Vilsmeier aromatization product formed in 42% yield from **1h** (*Table 2*). Katritzky and his group[13,14] have reported that 4,6-dichloro-5-[(dimethylamino)methylene]-cyclohexa-3,6-diene-1,3-dicarbaldehyde, the tautomer of product **4c**, was formed as an intermediate in this reaction; however, only product **4c** was isolated in our work. 2,4-Dichlorobenzene-1,3,5-tricarbaldehyde (**4a**) was formed in all

Table 2

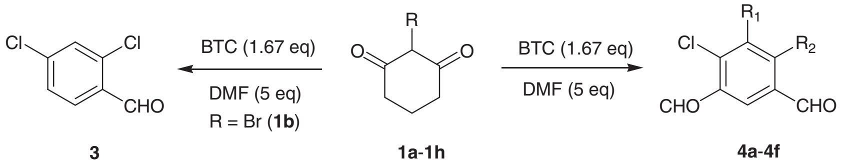
Synthesis of Substituted Aromatic Compounds under Vilsmeier Conditions[a]

Entry	R	Product	R^1	R^2	Yield (%)[b]
1	H (**1a**)	**4a**	CHO	Cl	54
2	$C_6H_5CH_2$ (**1b**)	**4a**	CHO	Cl	22
3	*p*-ClC_6H_4CO (**1c**)	**4a**	CHO	Cl	37
		p-$ClC_6H_4CO_2H$	—	—	30
4	C_6H_5CO (**1d**)	**4a**	CHO	Cl	35
		$PhCO_2H$	—	—	28
5	CH_2CO_2Et (**1e**)	**4b**	CH_2CO_2Et	OCHO	41
		4c	CH_2NMe_2	Cl	26
		4a	CHO	Cl	18
6	*n*-Bu (**1f**)	**4d**	*n*-Bu	OCHO	38
		4e	*n*-Bu	OH	20
		4a	CHO	Cl	15
7	*n*-Pr (**1g**)	**4f**	*n*-Pr	OCHO	47
		4a	CHO	Cl	17
8	Br (**1h**)	**3**	H	Cl	42

[a] Substrate **1** (5 mmol), BTC (8.33 mmol), DMF (25 mmol), 4.0 h. The reaction was carried out in refluxing 1,2-dichloroethane.
[b] Yield of isolated products based on 1,3-cyclohexanediones added.



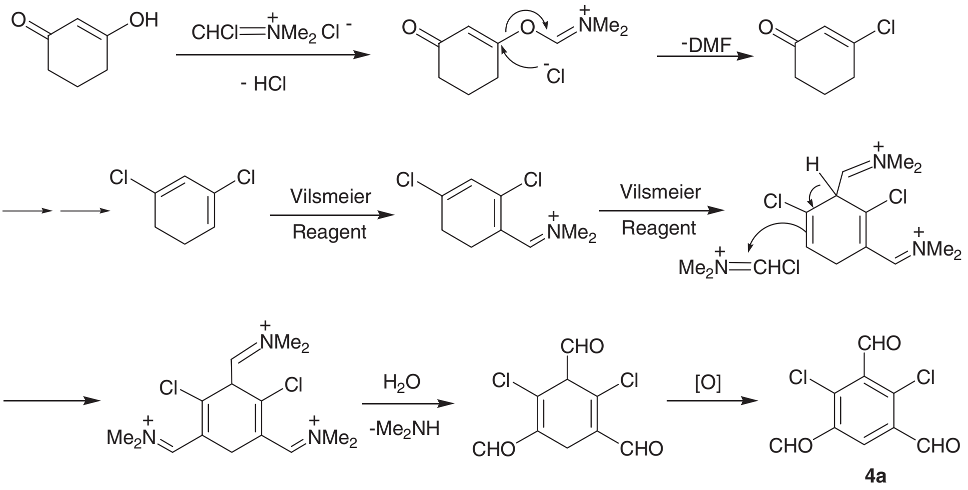
Scheme 1



Scheme 2

reactions except for **1b**. In addition to **4a**, benzoic acid and 4-chlorobenzoic acid were isolated in the case of 2-benzoyl-1,3-cyclohexanedione (**1c**) or 2-(4-chlorobenzoyl)-1,3-cyclohexanedione (**1d**) .

Although is possible to rationalize the generation of **4a** from **1a** as shown in *Scheme 3*, the mode of formation of **4a** from the other substrates remains unclear.



Scheme 3

Table 3
Spectral Data for Products

Cmpd.	MS (EI)	^{1}H NMR (δ)	^{13}C NMR (δ)
2	130 (M^+, 100), 132 (M^+ + 2, 33)	2.06–2.12 (m, 2 H, CH_2), 2.40 (t, 2 H, $J = 6.8$ Hz, CH_2), 2.69 (t, 2 H, $J = 6.0$ Hz, CH_2), 6.22 (s, 1 H, CH)	22.6, 33.8, 36.2, 128.4, 158.6, 196.8
3	174 (M^+, 100), 176 ($M^+ + 2$, 67), 178 ($M^+ + 4$, 11)	7.37 (d, 1 H, $J = 6.8$ Hz, Ar H), 7.49 (s, 1 H, Ar H), 7.87 (d, 1 H, $J = 8.4$ Hz, Ar H), 10.42 (s, 1 H, CHO)	128.2, 130.5, 130.7, 131.1, 138.4, 141.3, 188.7
4a	230 (M^+, 100), 232 ($M^+ + 2$, 67), 234 ($M^+ + 4$, 11)	8.58 (s, 1 H, Ar H), 10.54 (s, 3 H, CHO)	132.4, 132.7, 133.7, 143.0, 186.8, 187.2
4b	298 (M^+, 11), 211 (100), 213 (33)	1.27 (t, 3 H, J = 7.0 Hz, CH_3), 4.20–4.25 (m, 2 H, CH_2), 4.84 (s, 2 H, CH_2), 8.61 (s, 1 H, Ar H), 10.50 (s, 1 H, CHO), 10.52 (s, 1 H, CHO), 10.61 (s, 1 H, CHO)	10.0, 61.8, 73.3, 127.5, 129.4, 129.9, 134.7, 145.6, 164.6, 168.0, 186.8, 187.6, 187.7
4c	259 (M^+, 23), 261 ($M^+ + 2$, 15), 263 ($M^+ + 4$, 2.5), 58 (100)	2.32 (s, 6 H, CH_3), 3.59 (s, 2 H, CH_2), 8.20 (s, 1 H, Ar H), 10.49 (s, 1 H, CHO), 10.53 (s, 1 H, CHO)	45.5, 59.8, 131.5, 132.8, 133.5, 136.7, 138.3, 141.2, 188.1, 188.6
4d	268 (M^+, 11), 184 (100), 186 (33)	1.01 (t, 3 H, J = 7.5 Hz, CH_3), 1.47–1.55 (m, 2 H, CH_2), 1.85–1.91 (m, 2 H, CH_2), 4.17 (t, 2 H, J = 6.5 Hz, CH_2), 8.54 (s, 1 H, Ar H), 10.36 (s, 1 H, CHO), 10.50 (s, 1 H, CHO), 10.53 (s, 1 H, CHO)	13.7, 18.9, 31.8, 80.1, 128.6, 129.0, 129.2, 133.9, 144.5, 166.9, 187.0, 187.1, 187.7
4e	240 (M^+, 45), 242 ($M^+ + 2$, 15) 183 (100)	1.02 (t, 3 H, J = 7.5 Hz, CH_3), 1.52–1.57 (m, 2 H, CH_2), 1.86–1.91 (m, 2 H, CH_2), 4.18 (t, 2 H, J = 6.5 Hz, CH_2), 7.04 (s, 1 H, Ar OH), 8.41 (s, 1 H, Ar H), 10.33 (s, 1 H, CHO), 10.41 (s, 1 H, CHO)	13.7, 19.1, 30.7, 69.5, 114.2, 123.9, 125.8, 130.8, 144.7, 164.6, 187.7
4f	254 (M^+, 7), 184 (100), 186 (33)	1.07 (t, 3 H, J = 7.5 Hz, CH_3), 1.90–1.95 (m, 2 H, CH_2), 4.13 (t, 2 H, J = 7.0 Hz, CH_2), 8.55 (s, 1 H, Ar H), 10.37 (s, 1 H, CHO), 10.50 (s, 1 H, CHO), 10.53 (s, 1 H, CHO)	10.2, 23.2, 81.7, 128.6, 129.0, 129.3, 133.9, 144.6, 166.8, 187.0, 187.1, 187.7

Table 4
Mps and Combustion Analyses

Cmpd.	mp (°C) (*lit*. mp.)	EA of new Compounds (found)
2	dense yellow oil[23]	—
3	yellow crystal 71–72 (68–70[13])	—
4a	yellow crystal 104−105 (104−106[13,14])	—
4b	white crystal 127.5–128.7	C, 52.28 (52.26); H, 3.71 (3.76)
4c	dense yellow oil[24]	—
4d	dense yellow oil	C, 58.11 (58.02); H, 4.88 (4.96)
4e	dense yellow oil	C, 59.88 (59.73); H, 5.44 (5.53)
4f	dense yellow oil	C, 56.59 (56.49); H, 4.35 (4.42)

In conclusion, although the yields of **3** from **1h** and of **4a** from **1a** are moderate, these compounds are obtained in *one step* from simple starting materials instead of the several steps that might be required to prepare them otherwise.

Experimental Section

Melting points were obtained on a Büchi B-540 melting point apparatus and uncorrected. Infrared spectra were recorded on a Thermo Nicolet Avatar 370 spectrophotometer. The NMR spectra were measured with a Bruker Advance III 500 or Varian Mercury plus-400 spectrometer in $CDCl_3$ using TMS as internal standard. Chemical shifts (δ) are expressed in ppm and coupling constants J are given in Hz. Mass spectra were obtained on a Finnigan Trace DSQ mass spectrometer. Elemental analysis was determined on a Carlo-Erba 1108 instrument. The starting materials 1,3-cyclohexanediones **1** were prepared according to the literature [21,22]. Organic solvents were obtained from commercial sources.

Preparation of 3-Chlorocyclohex-2-enone (2)

A solution of 1,3-cyclohexanedione **1a** (0.56 g, 5 mmol) in 1,2-dichloroethane (10 mL) was added dropwise to an ice-cooled magnetically stirred mixture of Vilsmeier reagent prepared from BTC (0.50 g, 1.67 mmol) and DMF (0.36 g, 5 mmol;) in 1,2-dichloroethane (20 mL). The reaction mixture was gradually allowed to attain room temperature, and the mixture was heated at reflux for 4 h. The residual solution was poured into crushed ice, stirred for 1 h, and extracted with ethyl acetate (3 × 30 mL), The organic layer was separated, washed with water, saturated $NaHCO_3$ and dried over Na_2SO_4. Evaporation of the solvent, followed by purification of the residue by silica gel column chromatography (petroleum ether/AcOEt 10:1) gave the product.

The preparation of 2,4-dichlorobenzaldehyde (**3**) was performed following the procedure described above but with BTC (1.49 g, 5 mmol) and DMF (1.09 g, 15 mmol).

Preparation of Compound 4a. Typical Procedure

A solution of 1,3-cyclohexanedione (**1a**) (0.56 g, 5 mmol) in 1,2-dichloroethane (20 mL) was added dropwise to an ice-cooled magnetically stirred mixture of Vilsmeier reagent prepared from BTC (2.50 g, 8.33 mmol) and DMF (1.82 g, 25 mmol) in 1,2-dichloroethane (30 mL). The reaction mixture was gradually allowed to attain room temperature and the mixture was heated at reflux for 4 h. The cooled solution was then poured into crushed ice, stirred for 1 h, extracted with $CHCl_3$ (3 × 30 mL), concentrated, and chromatographed on silica gel (petroleum ether/EtOAc 8:1) to give the corresponding products (*Tables 2 and 3*).

Acknowledgement

We are grateful to National Natural Science Foundation of China (No. 20676123) for financial support.

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